Remarks

The applicants responded completely to each point of the rejection in the previously filed amendment/response filed on March 22, 2010. The applicants hereby present amended claims and new claims. **The single independent "product by process" claim present in the previous response of March 22, 2010, claim 91, has not been amended in the present supplemental amendment/response.** New process claims have been presented. **These newly presented process claims are, however, all related to the previously claimed product by process invention of claim 91.**

New "process of making" claims (independent process of making claim 236 and dependent claims 237-299) are directed to processes of making the previously claimed "product by process" inventions claimed by independent product by process claim 91. These new "process of making" claims (claims 236-299) are directed to the process recited in product by process claim 91. In addition, as stated previously, the applicants have limited the scope of claim 91 to products produced by the recited process or an equivalent process, (see p. 71 of the Amend./Resp. of 3/10/2009 and p. 30 of the Amend./Resp. of 3/22/2010). Therefore, the product by process claimed in claim 91 cannot be made by a process which is substantially different than the process recited in claim 91. Similarly the product by process claimed in claim 91 cannot be made by a process which is materially different than the process of making claims of claims 236-299. And the process of making claims of claims 236-299 cannot be used to make a product that is materially different than the product by process of claim 91. **Therefore the product by process claims of claim 91 and process of making claims 236-299 should not properly be subject to a restriction requirement as these claims do not meet the criteria for distinctness.** See MPEP 806.05(f), the product by process claims of claim 91 and process of making claims 236-299 do not meet either of criteria (A) or (B), *"(A) that the*

process as claimed is not an obvious process of making the product and the process as claimed can be used to make another materially different product; or (B) that the product as claimed can be made by another materially different process."

New process of using claims 299-302 are presented. These new process of using claims refer to and include all the limitations in product by process claim 91. Therefore these process of using claims 299-302 should not be subject to restriction or should be eligible for rejoinder. Applicants submit that claim 91 and claims 299-302 do not meet the criteria for distinctness under MPEP 806.05(h).

New independent process of making claims 303-307 are presented. The applicants submit that process of making claims 303-307 and new process of making claims 236-299 are not properly subject to restriction because these claims meet the criteria of MPEP 806.05(c) I. Subcombination essential to combination. More specifically "the set of oligonucleotides" in independent claim 303 is included in the "set of oligonucleotides" in independent claim 236. And the other limitations in claim 236 and claim 303 are essentially identical. **Therefore the combination of claim 236 requires the details of the subcombination of claim 303.**

Support for limitations in the claims in the present claim set

Support for the limitations in the claims of the previous Amendment/Response of March 10, 2009 was cited on pp. 51-70 of that previous Amendment/Response. The limitations in the presently pending claims are, in general, not new and are the same or essentially the same, as limitations in the claim set of March 10, 2009. Therefore the Examiner is urged to consult the Remarks of previous Amendment/Response of March 10, 2009 on pp. 51-70 for detailed support in the present application 10/037,718, the PCT parent PCT/US99/04376, and Provisional priority application 60/076102 in terms of page and line number. In addition the Examiner is urged to consult similar detailed support for some claim limitations in the Remarks of the Brief Supplemental Response of July 3, 2009,

pp. 2-5. Also similar detailed support for some claim limitations is present in the Remarks of the Preliminary Amendment of October 2, 2007, pp. 15-37.

For the Examiner's convenience, the applicants will now cite support for new claims to help ensure compliance with the Written Description Requirement of 35 U.S.C. 112.

The applicants will now cite support for limitations in the presently pending claims. The cited support will be in accordance with the Written Description Requirement; MPEP 2163 states in part: *"To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.*

The PCT parent, PCT/US99/04376 (filed 2/26/99), claims priority from Provisional priority application 60/076102 (filed 2/26/98). And each of the later filed parent U.S. National applications for the present application, 09/623068 filed 8/26/2000 and 09/947768 filed 9/5/2001, incorporate by reference the earlier filed PCT parent, PCT/US99/04376. The present application 10/037,718 also claims priority from Provisional priority application 60/076102.

Cited support for the limitations in the presently pending claims will cite specific parts of the present application 10/037,718, the PCT parent PCT/US99/04376, and Provisional priority application 60/076102. In most or all cases the page and line numbers of the relevant sections of these applications will be cited. **For the sake of brevity the following abbreviations will be used:** "'718 app." for the present application 10/037,718, "PCT" for the PCT parent PCT/US99/04376, and "Prov. '102" for Provisional priority application 60/076102.

Support for limitations in independent claim 236

Remarks in support of claim 236 are longer and more detailed, Remarks in support of the other (dependent) claims are generally shorter and less detailed.

Support for independent process of making claim 236 As noted previously, previously pending claim 91 is a product by process claim and support has already been cited for this product by process claim on pp. 51-57 of the previous Amendment/Response of March 10, 2009. For further support of the process of making in terms of complementary oligonucleotides included in a composition, see for example, '718 app. p. 34 line 25 to p. 35 line 16, p. 35 line 24 to p. 36 line 27, p. 37 line 3 to line 22, p. 48 lines 6-8, lines 12-16, PCT p. 33 line 20 to p. 34 line 11, p. 34 line 19 to p. 35 line 22, p. 35 line 37 to p. 36 line 17, p. 47 lines 6-8, lines 12-16, and Prov. '102 p. 64 lines 41-52, p. 60 lines 33-46, p. 52 line 46-53, p. 53 line 12 to p. 54 line 22, p. 54 lines 6-8, and p. 53 lines 42-52.
In addition, various "acts of making" using complementary oligonucleotides are described in papers that are incorporated by reference into each of the patent applications that are in the endnotes of '718 app. pp. 49-50, PCT p. 48, and Prov. '102 p.125. These references also describe examples using specific oligonucleotides in terms of specific nucleotide sequences, i.e. specific structure. **See specifically the references below. These references were previously submitted in Information Disclosure Statements, specifically the Chee reference (1) is listed as reference D1 in the Information Disclosure Statement of 5/19/2008 and a copy of the Chee reference was provided to the Examiner. And the other references are listed in the IDS of June 2009 as references AH-AM on sheets 1 and 2.**

(1) Accessing Genetic Information with High-Density DNA Arrays, Mark Chee, et al. Science, vol 274, Oct. 25, 1996 , pp. 610 – 614. See for example, p. 610 top right, and PCR amplification in endnotes (12), (13) & (20) pp. 613 & 614, an example of specific oligonucleotide sequence information is on p. 611.

(2)Genetic analysis of amplified DNA with immobilized sequence- specific oligonucleotide probes, Saiki,et al. Proc Natl Acad Sci USA vol 86, pp.6230-6234. See for example, p. 6231 & 6230, an example of specific oligonucleotide sequence information is on p. 6232.
(3)Allele-specific enzymatic amplification of β-globin genomic DNA for diagnosis of sickle cell anemia, Wu, et al., Proc Natl Acad Sci USA vol 86 pp 2757-2760. See for example, p. 2758 & 2760, an example of specific oligonucleotide sequence information is on p. 2757 & 2758 in terms of PCR primers and in terms of normal and sickle cell alleles.
(4)Automated DNA diagnostics using an Elisa-based oligonucleotide ligation assay, Nickerson, et al., Proc Natl Acad Sci USA vol 87, pp. 8923-8927. See for example, p. 8923 & 8924, also p. 8927, an example of specific oligonucleotide sequence information is on p. 8925.
(5)Schuster, H. et al (1995) Nature Genetics, 13(1) : 98 – 100. See for example, p. 100, an example of specific oligonucleotide sequence information is on p. 98 in terms of specific alleles.
(6)Gyapay, G. et al (1994) Nature Genetics, 7: 246-339. See for example, p. 246 & 248.

(The Wang reference (7) is incorporated by reference into PCT and '718 app. (8) Large Scale Identification, Mapping, and Genotyping of Single-Nucleotide Polymorphisms in the Human Genome, Wang, et. al., Science, May 15, 1998, vol 280, pp. 1077-1081.) See for example, endnotes 25 & 26 on p. 1082.

For support for the limitation *"choosing a group of covering markers so that a CL-F region is N-covered to within [x, y] by the covering markers, wherein [x, y] is a two-dimensional distance....N is an integer greater than or equal to 1."* This limitation was present in dependent claims in the previous claim set filed May 1, 2008, so it really is not new. For support see for example, '718 app. p.14 lines

26-28, lines 33-37, PCT p. 13 lines 26-28, lines 33-37, and Prov. '102 p. 30 lines 45-47, lines 52-53, & p. 31 lines 2-4.

For support for the limitation *"wherein x is less than or equal to 1 million base pairs and y is less than or equal to 0.2"* see for example '718 app. p.27 lines 20-23, lines 27-28, 32-33, p. 29 lines 16-17; PCT p. 26 lines 11-14, lines 18-20, p. 28 lines 7-8 and Prov. '102 p. 35 lines 14, 20-22, 44-46, p. 40 lines 18-20.

For support for the limitation *"whereby each point in the region is within the distance [x, y] of each of N or more of the covering markers."* This whereby clause is not a true limitation, it follows from the other limitations in the claim and the definition of N-covering. See '718 app. p. 13 lines 34-36 & p. 14 lines 26-28, PCT p. 12 lines 34-36 & p. 13 lines 26-28 and Prov. '102 p. 30 lines 19-21, lines 45-47.

For support for the limitation *"wherein the CL-F region is a segment-subrange."* This limitation was present in the previous claim set of May 1, 2008, so the limitation is not new. For support see '718 app. p. 15 lines 19-20, p. 28 lines 4-5; PCT p. 14 lines 19-20, p. 26 lines 34-35 and Prov. '102 p. 27 lines 15-17, p. 40 lines 44-48, p. 72 lines 37-38. The whereby clause *"whereby the segment-subrange is a rectangular region on the CL-F map"* is not a true limitation. This whereby clause follows from the Description, see '718 app. p. 15 lines 19-20, PCT p. 14 lines 19-20 and Prov. '102 p. 27 lines 15-17. The limitation *"whereby the segment-subrange is bounded by a chromosomal segment and a least common allele frequency subrange"* is not a true limitation, but follows from the definition of segment-subrange; see '718 app. p. 15 lines 17-33, PCT p. 14 lines 17-33, and Prov. '102 p. 27 lines 3-38, and p. 31 lines 5-7.

For support for the limitation *"wherein the length of the segment of the segment-subrange is greater than or equal to the length of human chromosome*

21." The application, PCT parent and Provisional priority application describe the segment of a segment-subrange as any length up to the length of an entire chromosome. And individual human chromosomes 1-22, X and Y are described. An example of the chromosomal location coordinates of CL-F points ranging over an entire chromosome, e.g. chromosome number 6, is given. Frequency subranges and chromosomal segments are described. See for example, '718 app. p. 14 lines 2-6, lines 10-13, p. 38 lines 29-30, p. 44 lines 26-27; PCT p. 13 lines 2-6, lines 10-13, p. 37 lines 15-16, p. 43 lines 26-27 and Prov. '102 p. 30 lines 27-30, lines 38-39, p. 40 lines 44-48, and p. 72 lines 37-38.

Each of chromosomes human chromosomes 1-22, and X and Y, including human chromosome 21, is thus an example of a described possible segment (and segment length) of a segment-subrange. The length of each of these example chromosomes is greater than or equal to the length of human chromosome 21, the shortest human chromosome. As stated above, the segment of a segment-subrange is described as any length up to the length of any chromosome. **And the example length of human chromosome 21 then acts as a described "range endpoint" for segment length as in the case In re Wertheim.** See for example, MPEP 2163.05 III. Range Limitations *"In the decision in In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of '25%- 60%' and specific examples of '36%' and '50%.' A corresponding new claim limitation to "at least 35%" did not meet the description requirement because the phrase "at least" had no upper limit and caused the claim to read literally on embodiments outside the "25% to 60%" range, however a limitation to 'between 35% and 60%' did meet the description requirement."*

For support for the limitation *"whereby the length of the segment is greater than or equal to about 47 million base pairs"* is not a true limitation, but follows from the limitation immediately above. The length of human chromosome 21 is known to be at or about 47 million base pairs. Human chromosome 21 is also

known to be the shortest human chromosome. The applicants will supply the Examiner with information from the National Library of Medicine and NIH that was reviewed in June 2008 that says: *"Chromosome 21 is the smallest human chromosome, spanning about 47 million base pairs."* An estimate of a length of 51 million base pairs for human chromosome 21 is given and a statement that it is *"the smallest of human autosomes"* (p. 119, vol. 2) in the 1996 Edition of Encyclopedia of molecular biology and molecular medicine, Editor Robert A. Meyers. An estimate of 46 cM is given (p. 563, vol. 3) in the Encyclopedia of molecular cell biology and molecular medicine (2nd Edition, 2004) Editor Robert A. Meyers.

For support for the limitation *"wherein the subrange of the segment-subrange includes the least common allele frequency 0.1,"* A polymorphism with least common allele frequency p = 0.1 has a very prominent role in the description as a sought (or target) disease (or trait-causing) polymorphism that is sought by two-dimensional association based linkage studies described in the application. For example as noted above, all of the calculations in Table 2 are based on p = 0.1. See Theory of Operation Sections of '718 app. p. 41, p.42 line 3, PCT p. 40, p. 41 line 3, and Prov. '102 p. 37 lines 24 & lines 46-55, p. 38 lines 7-8 and p. 82 lines 8-10. More specifically in Table 2 the disease allele's frequency is fixed at p=0.1 while the frequency (m) of the positively associated marker allele varies (m = .5, .3, .2, .1, .05) see Theory of Operation Sections of '718 app. p. 40 lines 10-12, PCT p. 39 lines 1-2, and Prov. '102 p. 37 lines 24 & lines 46-55, p. 38 lines 7-8 and p. 82 lines 8-10.

This description also leads to the description of using lower heterozygosity (lower minor allele frequency, less than or equal to about 0.3, that are "close to 0.1"), markers, rather than just higher heterozygosity markers. See for example '718 app. p. 44 lines 1-2, PCT p. 43 lines 1-2, and Prov. '102 p. 14 lines 14-16.

Thus it is clear that the '718 app., PCT and Prov. '102 describe the least common

allele frequency p = 0.1 as a place to look for a trait-causing (e.g., disease) polymorphism on a CL-F map. The present application also describes *"… a rectangular CL-F region, a segment-subrange, that is N covered is used in an association based linkage study to test for the presence of a trait causing bi-allelic gene located within the segment-subrange."* See '718 app. p. 28 lines 5-6, PCT p. 26 lines 34-36, and similar concepts are in Prov. '102 p. 16 lines 49-50, p. 17 lines 4-7, p. 20 lines 2-6. Therefore the present application, (and PCT parent and priority applications) describe a CL-F region that is a segment-subrange that contains the least common allele frequency p = 0.1. (It should be noted the terms "gene" and "trait-causing polymorphism" mean the same thing, see '718 app. p. 1 lines 34-36, PCT p. 1 lines 20-22, and Prov. '102 p. 25 lines 15-19.)
As an example, the Theory of Operation, set/subset example(s) describe covering rectangular CL-F region(s), segment-subrange(s), that include the least common allele frequency p = 0.1; see for example '718 app. pp. 44-47, PCT pp. 43-46, and Prov. '102 p. 75 line 26 to p. 76 line 50, especially lines 36-50.

For support for the limitation *"whereby there are at least about 24 covering markers with least common allele frequencies less than or equal to 0.3 that are distributed within the segment with a density of at least about 1 marker every two million base pairs,"* this "whereby clause" is not a true limitation but necessarily follows from other limitations in the claim.

The least common allele frequencies of covering markers in the whereby clause being less than or equal to 0.3 necessarily follows because *"y is less than or equal to 0.2"* and the segment-subrange contains the minor allele frequency p = 0.1. That is, $p + y \leq 0.3$.

The density of covering markers in the whereby clause being at least about 1 marker every two million base pairs necessarily follows because *"x is less than or equal to 1 million base pairs."* The minimum density of the markers distributed within the segment in the whereby clause is equal or about equal to 1 marker

every 2 times x; 2 times x is 2 million base pairs. This yields a minimum density of at least, or at least about, 1 marker every 2 million base pairs.

The number at least about 24 covering markers in the whereby clause necessarily follows from dividing the length of human chromosome 21 (about 47 million base pairs) by the density (about 1 marker every 2 million base pairs). This yields the number about 23.5. Since there is no such thing as 1/2 of a marker, the number is rounded up to 24.

For support for the limitation *"selecting the set of oligonucleotides for the set's utility to determine genotype data or sample allele frequency data for each of the two or more covering markers"* see '718 app. p. 37 lines 8-22, PCT p. 36 lines 3-17, and Prov. '102 p. 64 lines 42-50. (It should be noted that genotype data for *"samples of individuals"* that are *"groups of individuals who have supplied phenotype data regarding the genetic characteristic and provided chromosomal DNA samples which have been pooled"* is sample allele frequency data; see for example Prov. '102 p. 36 lines 23-34.)

For support for the limitation *"including the one or more copies of the set of oligonucleotides in the composition"* see for example, '718 app. p. 34 line 25 to p. 35 line 37, p. 37 line 3 to line 22, p. 48 lines 6-8, lines 12-16, PCT p. 33 line 20 to p. 34 line 32, p. 35 line 37 to p. 36 line 11, p. 47 lines 6-8, lines 12-16, and Prov. '102 p. 64 lines 41-52, p. 52 line 45 to p. 54 line 23, p. 54 lines 5-8, and p. 53 lines 42-52.

Various acts of making are included in papers (references (1)-(7)) that are incorporated by reference into each of the patent applications that are in the endnotes '718 app. pp. 49-50, PCT p. 48, and Prov. '102 p.125. As stated above the Chee reference (1) is listed as reference D1 in the Information Disclosure Statement of 5/19/2008 and References (2)-(7) were included in the IDS of June 2009 as references AH-AM on sheets 1 and 2. More details on these references (1)-(7) are given above.

Support for dependent process of making claims 237-252, the limitations in these claims are generally the same or essentially the same as those in claims 108-235 of the claim set filed on March 10, 2009. Detailed support for these claims is given on pp. 58-68 of the Amendment/Response of March 10, 2009. The Examiner is urged to consult these pages. These pages describe detailed support for various claimed subranges and segments that defined various claimed segment-subranges, various claimed values for "x" and "y," and values for "N," the human species, and various "whereby clauses" used as limitations in claims 237-252.

Support for the limitation *"wherein the chosen group of covering markers includes thousands of bi-allelic markers"* in claims 250-252, is found on bottom of p. 61 to p. 63 in the Remarks of the Amend./Resp. of 3/10/2009 under old claims 171-178.

Support for dependent process of making claims 253-268 that recite "a sensor," see '718 app. p. 34 line 25 to p. 35 line 7, especially p. 34 line 31 to p. 35 line 7, PCT p. 33 line 20 to p. 34 line 2, especially p. 33 line 31 to p. 34 line 2, and Prov. '102 p. 53 lines 10-35, especially lines 16-28.

Support for dependent process of making claims 269-279 that recite "type (1) complementary oligonucleotides that are allele-specific," see pp. 19-20 of the Remarks in the Preliminary Amendment of October 2, 2007 under old claim 92. See also '718 app p. 21 lines 19-34, p. 48 lines 5–8, PCT p. 20 lines 11-25, p. 47 lines 5-8, and Prov. '102 see for example, p. 28 lines 46-51, p. 53 lines 41-46. See also endnotes ('718 app. p. 50, PCT p. 48, Prov.'102 p. 125) with the endnote on the Saiki reference that recites the title *"Genetic analysis of amplified DNA with immobilized sequence- specific oligonucleotide probes."*

Support for dependent process of making claims 280-290 that recite "an array" see bottom of p. 67 to top p. 68 under old claims 201-211 in the Remarks of the Amend./Resp. of 3/10/2009.

Support for dependent process of making claims 291-299 that recite "an array" see bottom of p. 68 under old claim 212 in the Remarks of the Amend./Resp. of 3/10/2009.

Support for independent process of using claim 300 see '718 app. p. 35 line 35 to p. 37 line 2, especially p. 36 line 17 to p. 37 line 2, PCT p. 34 line 30 to p. 35 line 36, especially p. 35 line 12 to p. 35 line 36, and Prov. '102 p. 60 line 32 to p. 61 line 52, especially p. 61 lines 41-52.

Support for independent process of making claim 303, as previously noted the limitations in this claim are almost the same as the limitations in independent process of making claim 236. Therefore see above under support for claim 236. Claim 303 differs from claim 236 in that the limitation *"there is an oligonucleotide in the set that is complementary to each of one or more alleles of each marker in the group of two or more bi-allelic covering markers"* in claim 303 is essentially substituted for the limitation *"wherein the set of oligonucleotides is complementary to the group of two or more bi-allelic covering markers"* in claim 236. For support for this substitution in claim 303, see '718 app. p. 35 line 35 to p. 37 line 2, especially p. 36 line 17 to p. 37 line 2; see also p. 34 lines 25-32. PCT p. 34 line 30 to p. 35 line 36, especially p. 35 line 12 to p. 35 line 36; see also p. 33 lines 20-27; and Prov. '102 p. 52 line 36 to p. 53 line 36, and p. 60 line 32 to line 44. See also support below for dependent claims 304, 305 & 307.

Regarding support for dependent claims 304, 305 & 307, see for example, see '718 app. p. 48 lines 3, 6-8, & 12-15; PCT p. 47 lines 3, 6-8, & 12-15; and Prov. '102 p. 53 lines 38-41, 43-47, & 48-51.

Supplemental Response Regarding Rebuttal of the Enablement Rejection

The applicants presented a rebuttal of the enablement rejection on pp. 17- 29 of the previous Amendment/Response of March 22, 2010. The applicants hereby supplement that rebuttal, with respect to the enablement made by the Set/Subset teaching as described on pp. 25-26 of the previous Amendment/Response of March 22, 2010. The Set/Subset teaching is given in the present application ('718 app.) on p. 44 line 4 to p. 47 line 32; in PCT p. 43 line 4 to p. 46 line 32 as the "Best Mode" and in Prov. '102, for example on p. 73 line 48 to p. 80 line 12.

As noted on pp. 25-26 of the Amendment/Response of 3/22/2010 in the

Set/Subset teaching a chromosome or chromosomal segment is completely covered by segments that are, for example, 7 –10 cMs, or less than 1 cM, or 250, 000 base pairs in length. Within each segment, there are subsets of (covering) markers. Thus each point on the chromosome or chromosomal segment is within a small (e.g., 10cM, 7cM, 1cM or 250,000 bp) chromosomal distance (along the CL axis or x-axis) of covering markers. And each subset of (covering) markers contains only markers having least common allele frequencies that are approximately the same (e.g., about 0.1, 0.2, 0.3, 04. & 0.5). It is clear then that subsets with approximately the same least common allele frequencies (e.g., about 0.1, 0.2, 0.3) N-cover segment-subranges to within [x, y], where $N \geq 2$, x = 10cM, 7cM, 1cM or 250, 000 bp, and y is various values such as ≤ 0.1, ≤ 0.15, ≤ 0.2. These N-covered segment-subranges are bounded by an entire chromosome or chromosomal segment and by a low frequency subrange such as, for example, 0 to 0.1, 0.1 to 0.2 or 0 to 0.2. A person of ordinary skill in the art would find it obvious (and thus enabling) to adjust the values of "N", [x, y], and the approximate least common allele frequencies of the subsets. **Thus the Set/Subset Example teaching that is present in the instant application '718 app., and priority applications PCT and Prov. '102 enable the general N-covering of segment-subranges.**

Supplemental Response Regarding Evidence of Unexpected Results

On pages 34-40 of the previously filed Amendment/Response of March 22, 2010, the applicants presented a **Rebuttal of the rejection of the applicants' arguments regarding unexpected results.** That rebuttal included many power calculations. **The applicants hereby present further power calculations in the form of a Table that is just below in this present response. This Table entitled "Full Power Table" corresponds to actual power calculations for the P_t values in Table 2 on page 41 of the present application and in the same Table 2 on page 40 of the PCT parent, PCT/US99/04376.** This Full Power Table (just below) is further evidence that the power of association-based

linkage studies depends on marker allele frequency. And this is further evidence that power for bi-allelic markers with lower minor allele frequencies is higher for bi-allelic markers with higher minor allele frequencies in some situations. This was an unexpected result around the time of filing. Bi-allelic markers with higher minor allele frequencies (e.g., near m = 0.5) are favored for use in linkage studies by the conventional art.

The TDT power calculations are done using "Method 2" (see Table 1 on p. 1343 in the published paper McGinnis AJHG (2000) vol. 67, pp.1340-1347; a copy of this published paper will be submitted herewith for the Examiner's convenience.) This is the same power calculation formula used in calculations in the patent applications and the inventor's paper (Annals of Human Genetics vol 62, pp. 159-179, 1998, referred to in previous responses "AHG98") that is incorporated by reference into the present application. The calculations in the Table assumes that there are 200 families each with two children having disease, that frequency of disease allele (p) is p=0.1 and that mode of inheritance in additive (midway between recessive and dominant).

After power reaches is maximum value (i.e. probability of 0.999≈1) increasing r, or δ or making m closer to p can no longer increase TDT power which has already "maxed out". However, to continue to show the effect on power of making m close p, calculations can be done with lower values of δ. As is clear values of $\delta = 0$ are associated with $P_t = 0.500$ and TDT power values of zero, see Table 2 on page 41 of the present '718 app. and on page 40 of PCT. To continue to show the effect on power of making m close p, calculations can be done using a more stringent significance level of 5x10E-08 or with lower values of p (e.g., lower than 0.1). However, the calculations already presented are more than adequate to demonstrate unexpected results.

Full Power Table

Magnitude of P_t and Corresponding Power at a significance level of 0.05

		δ_{max}			$(1/2)\delta_{max}$		
		P_t	H/F	TDT Power	P_t	H/F	TDT Power
r=2	m=0.5	0.526	0.499	0.178	0.513	0.5	0.075
	m=0.3	0.541	0.446	0.34	0.521	0.433	0.119
	m=0.2	0.558	0.365	0.509	0.531	0.343	0.175
	m=0.1	0.595	0.248	0.767	0.555	0.215	0.301
	m=.05	0.589	0.134	0.453	0.552	0.115	0.167
r=5	m=0.5	0.596	0.496	0.971	0.548	0.499	0.483
	m=0.3	0.633	0.498	0.999	0.572	0.461	0.792
	m=0.2	0.666	0.458	0.999	0.597	0.392	0.934
	m=0.1	0.719	0.389	0.999	0.648	0.288	0.996
	m=.05	0.696	0.217	0.999	0.636	0.157	0.871
r=10	m=0.5	0.656	0.491	0.999	0.577	0.498	0.87
	m=0.3	0.702	0.532	0.999	0.612	0.48	0.994
	m=0.2	0.736	0.519	0.999	0.644	0.425	0.999
	m=0.1	0.785	0.484	0.999	0.703	0.339	0.999
	m=.05	0.75	0.275	0.999	0.684	0.187	0.997
r=∞	m=0.5	0.74	0.481	0.999	0.617	0.495	0.997
	m=0.3	0.791	0.555	0.999	0.663	0.497	0.999
	m=0.2	0.826	0.566	0.999	0.703	0.455	0.999
	m=0.1	0.87	0.561	0.999	0.77	0.386	0.999
	m=.05	0.816	0.329	0.999	0.741	0.216	0.999

Conclusion

The applicants have filed a Supplemental Amendment/Response following the submission of a Request for an RCE and an Amendment/Response on March 22, 2010. The previously filed Amendment/Response of March 22, 2010 responded fully to the Final Rejection of 10/20/2009.

The single independent product by process claim 91 in the previously filed Amendment/Response of 3/22/2010 has not been amended in the present Supplemental Amendment/Response. Four product by process claims are still pending (independent claim 91 and amended dependent claims 92, 105 and 212). New claims 236-307 are presented, including three new independent claims (236, 300 and 303). Independent claims 236 and 303 are process of making claims and independent claim 300 is a process of use claim. The total number of pending claims is 76, unchanged from the previous total. The total number of pending independent claims is four, less than the maximum number previously paid for (8 or 9). Remarks and arguments have been made that the claimed inventions are not independent or distinct and thus should not properly be subject to restriction.

Remarks to indicate support for claim limitations and ensure compliance with the Written Description Requirement have been made. Supplemental response and remarks regarding enablement (and rebuttal of the previous rejection for lack of enablement) have been made. Supplemental response and remarks regarding evidence of unexpected results in the form of actual power calculations presented in a "Full Power Table" have been made.

For the reasons advanced above, applicants respectfully submit that the claims are now in condition for allowance and that action is earnestly solicited.

Respectfully submitted,

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Attachments:

MCGINNIS, *Am. J. Hum. Genet. (2000) 67:1340–1347,* General Equations for P_t, P_s, and the Power of the TDT and the Affected–Sib-Pair Test.